

FIGURE 1

FIGURE 2a. Primers used to obtain sequences high-fidelity PCR amplification of human cDNA.

5 RAPF: GCGATAGGATCCTACTCGCGGGAGAAGAACCAAGCCAGCCGTCCCCGA
RAPR: GCGATAAACCGGTTCTGCCTCGCGCGAGCTCTGGAGATCCTGCCGGACAGGTCT

GAAF: GCGATAACCGGTGCACACCCCGGCCGTCCCAGAGCAGTG
GAAR: GCGATAACTCGAGTCAACACCAAGCTGACGAGAAACTGC

10 IDUF: GCGATAACCGGTGAGGCCCGCACCTGGTGCATGTGGACGCCGC
IDUR: GCGATAACTCGAGTCATGGATTGCCGGGATGGGGGCCCTTGG

GDNF: ACAGTGACCGGTTACCAAGATAAACAAATGGCA
15 GDNR: ACAGTGCTCGAGTCTAGATCAGATACATCCACACCTTT

FIGURE 2b. GDNF fusion, substitution of RAPF with RAPBACF in RAP amplification of GDNF construct.

RAPBACF: ACAGTGGCCATGGGGGTTCTTACTCGCGGGAGAAGAACCAAGCCG
20

FIGURE 3. Nucleotide and protein sequences of the RAP-GAA fusion

cttaccgcccattgggggtccgagcggggctctgtggctgtccctggctctgcgcaccgtg
 M R G P S G A L W L L L A L R T V
 5 ctcggatcctactcgccggagaagaaccagcccaagccgtcccgaaacgcgagtcggaa
 L G S Y S R E K N Q P K P S P K R E S G
 gaggagttccgcatggagaagttaaccagctgtggagaaggcccagcactgcacatctt
 E E F R M E K L N Q L W E K A Q R L H L
 10 cctcccgtagggctggccgagctccacgcgtatctgaagatacaggagagggacgaactc
 P P V R L A E L H A D L K I Q E R D E L
 gccttggaaagaaactaaagcttgcggcttggacgaagatgggagaaggaagcgagactc
 A W K K L K L D G L D E D G E K E A R L
 atacgcaacactcaatgtcatcttggccaagtatggctggacgaaaagaaggacgctcg
 I R N L N V I L A K Y G L D G K K D A R
 15 caggtgaccaggcaactccctcagtggcacccaggaagacgggctggatgaccccaggctg
 Q V T S N S L S G T Q E D G L D D P R L
 gaaaagctgtggcacaaggcgaagacctctggaaattctccggcgaagaactggacaag
 E K L W H K A K T S G K F S G E E L D K
 20 ctctggggaggttcctgcatacataagagaaagttcacgactacaacgtcctgctggag
 L W R E F L H H K E K V H E Y N V L L E
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 T L S R T E E I H E N V I S P S D L S D
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 25 aaccagggcctggaccgcctgcccggcagggctacagcactgaggctgag
 N Q G L D R L R R V S H Q G Y S T E A E
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 F E E P R V I D L W D L A Q S A N L T D
 aaggagctggaggcgttccggaggagctcaagcacttgcagccaaatcgagaagcac
 K E L E A F R E E L K H F E A K I E K H
 30 aaccactaccagaagcagctggagattgcgcacgagaagctgaggcacgcagagac
 N H Y Q K Q L E I A H E K L R H A E S V
 ggcgcacggcgcagcgttgagccgcagccgcgagaagcacgcctgctggagggcggacc
 G D G E R V S R S R E K H A L L E G R T
 35 aaggagctgggctacacggtaagaagcatctgcaggacgttccggcaggatctccaga
 K E L G Y T V K K H L Q D L S G R I S R
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 Q C E A R G C C Y I P A K Q G L Q G A Q
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 M G Q P W C F F P P S Y P S Y K L E N L
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 55 gcggaccagttccctcagctgtccacccctgcgtccctgcagttatatacaggccctc
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 D L A P T P G A N L Y G S H P F Y L A L
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W N D L D Y M D S R R D F T F N K D G F
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R D F P A M V Q E L H Q G G R R Y M M I
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15 V D P A I S S S G P A G S Y R P Y D E G
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L R R G V F I T N E T G Q P L I G K V W
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P G S T A F P D F T N P T A L A W W E D
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P S N F I R G S E D G C P N N E L E N P
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R Y A L L P H L Y T L F H Q A H V A G E
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T V A R P L F L E F P K D S S T W T V D
caccagctcctgtgg
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E V T G Y F P L G T W Y D L Q T V P I E
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G Q W V T L P A P L D T I N V H L R A G
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Y I I P L Q G P G L T T T E S R Q Q P M
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55 A L A V A L T K G G E A R G E L F W D D
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G E S L E V L E R G A Y T Q V I F L A R
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60 N N T I V N E L V R V T S E G A G L Q L
cagaagggtactgtcctggcgtggccacggcccccacggccatggccatggccatgg
Q K V T V L G V A T A P Q Q V L S N G V

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P V S N F T Y S P D T K V L D I C V S L
ttgatgggagagcagttctcgtcagctggtgttactcgag
L M G E Q F L V S W C -

5

Melanotransferrin signal sequence is italicized. Linker peptide is underlined.

FIGURE 4. Nucleotide and protein sequences of the RAP-IDU fusion

aagcttaccgccatgcggggtccgagcggggctctgtggctgtccctggctcgccacc
 M R G P S G A L W L L L A L R T
 5 ·gtgctcgatccactcgccggagaagaaccagcccaagccgtcccccggaaacgcgactcc
 V L G S Y S R E K N Q P K P S P K R E S
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 G E E F R M E K L N Q L W E K A Q R L H
 cttcctcccgtagggctggccagctccacgctgatctgaagatacaggagagggacgaa
 10 L P P V R L A E L H A D L K I Q E R D E
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 L A W K K L K L D G L D E D G E K E A R
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 L I R N L N V I L A K Y G L D G K K D A
 15 cggcaggtgaccagcaactccctcagtggcaccaggaaagacgggctggatgacccagg
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 I N Q G L D R L R R V S H Q G Y S T E A
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 G A V P H R G I K Q V R T H W L L E L V
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 L D L L R E N Q L L P G F E L M G S A S
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 25 N G L C S P D G E W R R L G R P V F P T
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 L W T Y E I Q F S Q D G K A Y T P V S R
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 Y R V R A L D Y W A R P G P F S D P V P
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 Y L E V P V P R G P P S P G N P -

Melanotransferrin signal sequence is italicized. Linker peptide is underlined.

FIGURE 5. Nucleotide and protein sequences of the RAP-GDNF fusion

atgggggttcttactcgccggagaagaaccagcccaagccgtcccgaaacgcgagtcc
 M G G S Y S R E K N Q P K P S P K R E S
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 L A W K K L K L D G L D E D G E K E A R
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 L V S D K V G Q A C C R P I A F D D D L
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 S F L D D N L V Y H I L R K H S A K R C
 50 ggatgtatctgtatcaga
 G C I -

Linker peptide is underlined.

Figure 6. Characterization of the RAP-GAA fusion.

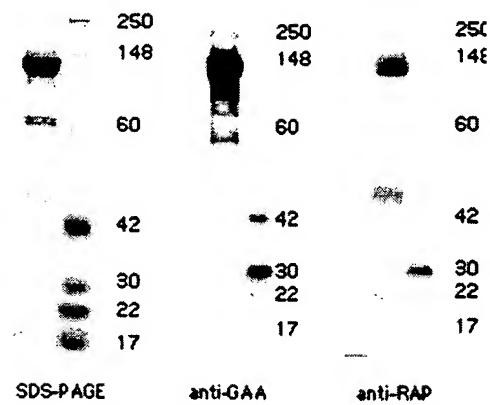


Figure 7. Assay for complex oligosaccharides on RAP-GAA

Digestion of RAP-GAA with Neuraminidase

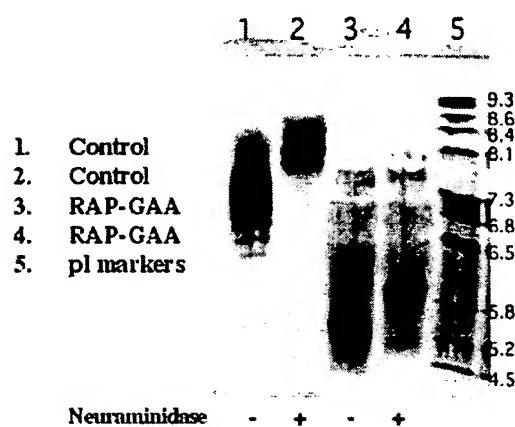


Figure 8. Assay for high-mannose oligosaccharides on RAP-GAA

Digestion of RAP-GAA with Endo H

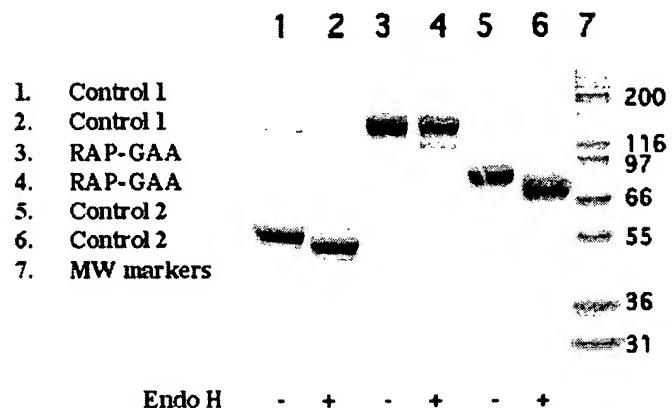
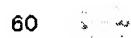
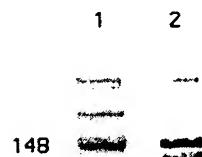


Figure 9. Characterization of RAP-IDU fusion

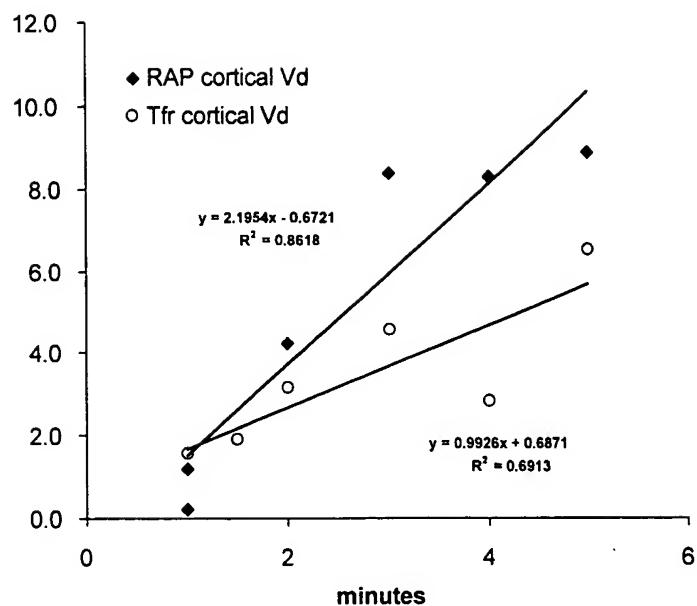


1. SDS-PAGE
2. Anti-Iduronidase Western

Binding of RAP and RAP-lysosomal enzyme fusion to LRP.

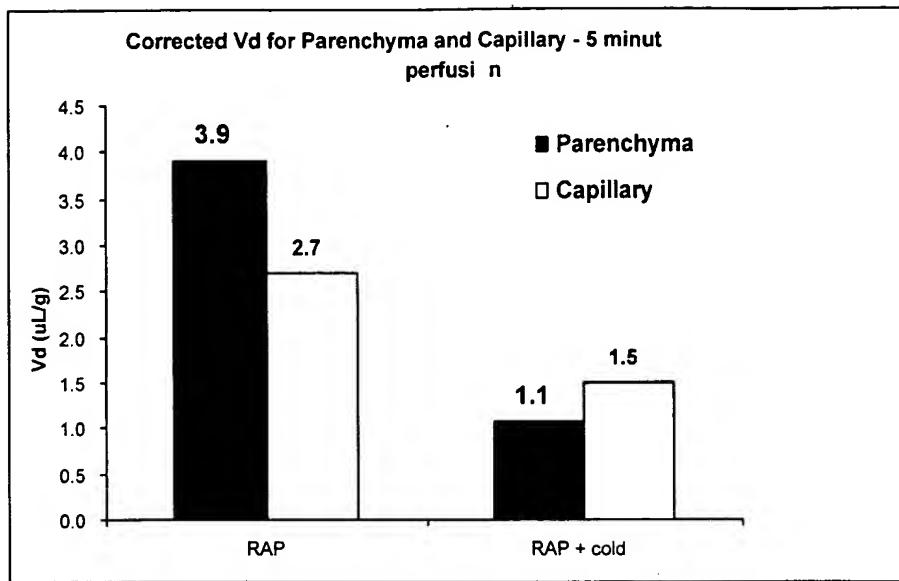
	None	RAP	RAP-Idu (Purified)	RAP-Idu (Medium)
Anti-RAP		●	■	●
Anti-Idu			●	●

FIGURE 10



Corrected V_d vs. Perfusion time.

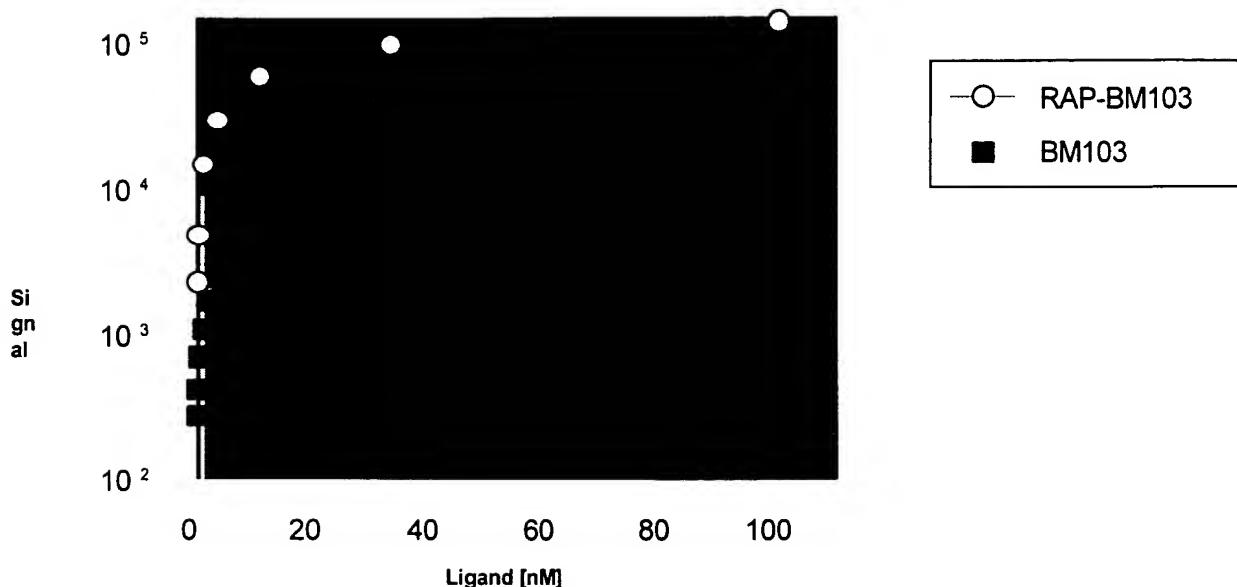
FIGURE 11.



Distribution of RAP between brain capillary endothelium and brain parenchyma.

FIGURE 12.

RAP-BM103 Uptake by Human Fibroblast
BM103 cells (GM244)



RAP-BM103

Parameter	Value	Std. Error
Vmax	160806	.4864
Km	18	.6316

BM103

Parameter	Value	Std. Error
Vmax	2691	.6376
Km	1	.6615

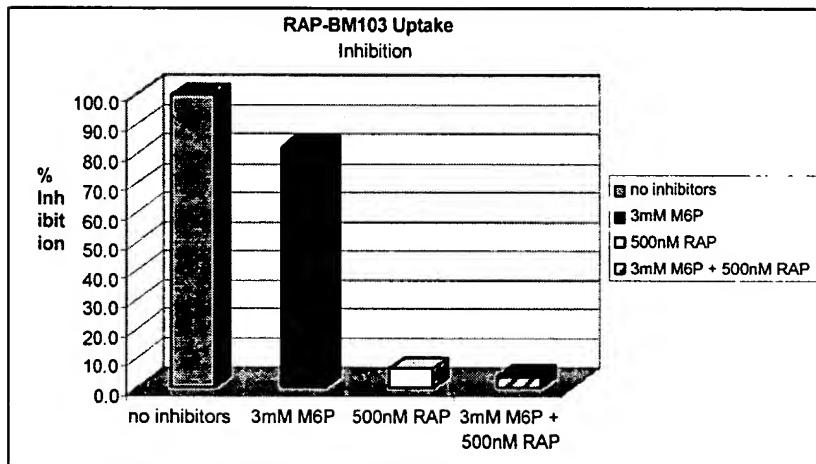


FIGURE 13

FIGURE 14. Multiple alignment of amino acid sequences of RAP from different species.

	human	1	-----MAPRRVRSFLRGLPA[RE]LILFLGPWPAAASHGGKYSREK	
5	mouse	1	MGGPTRPSPVSLALQRKMAPRERRVSTLPRLQLLV[RE]LIPMLVPQPIAGHGGKYSREK	
	rat	1	-----LRDRVSTLPRLQLLV[RE]LIPLLIVPQPIAGHGGKYSREK	
	chicken	1	-----MGATRT[VAVMAAFLAVSTRAS]KTYTRFA	
	zebrafish	1	-----MNGKYSREK	
	fruit fly	1	-----MVR[ALVVAIAAISV]VIALQGVADKKQSKYNSKEA	
10	mosquito	1	-----ELCPIARRKRGKIH[TL]TMLPFLTRCVTVFTVLCNVHQVSEAHSKY	
	flatworm	1	-----MRNHF[FLL]	
	consensus	1		t 1 11 1ml hggkysre
15	human	40	-----[QPKPSPKRESCE]FPRMEKLNC[WEKAQRLHLPPVRLAELHADLKIQE]RDE	
	mouse	61	-----[NEPEMAAKKRESCE]FPRMEKLNC[WEKAQRLHLPPVRLAELHSDLKIQE]RDE	
	rat	40	-----[NEPEMAAKKRESCE]FPRMEKLNC[WEKAQRLHLPPVRLAELHSDLKIQE]RDE	
	chicken	29	-----[NEG]LADAKP[REAGE]FPRV[ELNQVWEKAQRLQLSAV]KLAELHSDLKIQE]KDE	
	zebrafish	10	-----[NEKNASDN]NNQVEFRIAKLNQVWEKAQRLQLSAV[ELHSDLKIQE]KDE	
20	fruit fly	37	-----NDPHFQQVK[DE]KYDPDFESIQRPFRMAKLNIVWAKAQR[LTEP]EKLKSLYME[LK]H[DE]E	
	mosquito	48	-----SKHANALPDSEIYEPDFESIQRPFRMAKLNIVWTKAQR[LTEP]EKLKSLYTELK[H]DKEE	
	flatworm	10	-----FLLVIGSAHNKKTQYRTERI[F]IY[E]KALQHVTDRNQLARLEKE[ISGYDAIY]	
	consensus	61	ne kr g efRmeklNqvweKAqrl lspvrLaeLhsdLkqi[de]	
25	human	91	-----I[A]WKKKLKDGLDEDGEKEAKLIRNLNVILAKYGLDGK[K]DAROVTSN-----SISGTOE-----	
	mouse	112	-----I[N]WKKKLKVEGLDKDGEKEAKLIRNLNVILAKYGLDGK[K]DAROVTSN-----A[L]NEDTQ-----	
	rat	91	-----I[N]WKKKLKVEGLDGGEKEAKLIRNLNVILAKYGLDGK[K]DAROVTSN-----A[L]NEDTQ-----	
	chicken	80	-----I[S]WKKKLKAEGLGEDGEKEAKLRRN[INVIM]TKYGMN[K]D[SH]LTD[T]N-----YI[KDGTE]-	
	zebrafish	61	-----I[Q]WKKKLKAEGLGEDGEKEAKLRRN[INVIM]TKYGMN[K]D[SH]LTD[T]N-----LKDHEV[K]IG-----	
30	fruit fly	96	-----I[A]WQQLNSQHK[K]DGLNADELRRKLI[G]IMSSND[LEH]FDTQDTEKLKP[Y]KKFHEAE[R]-----	
	mosquito	107	-----I[T]YQNLK--EK[K]DGLNAELENK[VSIM]STV[G]I[LEH]FDTQDPEKYKLA[K]SSDGAPKKD-----	
	flatworm	61	-----I[A]SKNSN[QGTQGTKEIDSI]DDDK[GKII]EKY[G]IEKAVLAFKEKYKHKNLFQQT[DN]P-----	
	consensus	121	1 wKklk egld dgekeaklrrnlnvIlakYglgkkd v sn 1 e e	
35	human	144	-----[P]GLDOPRLEKLW[H]KAKTSGKFSGEELDKLWREFLHHKEK[V]HEY[N]V[L]LET[L]-----	
	mouse	165	-----[P]ELGOPRLEKLW[H]KAKTSGKFSSEELDKLWREFLHYKEKIQEYNV[L]LET[L]-----	
	rat	144	-----[P]ELGOPRLEKLW[H]KAKTSGKFSSEELDKLWREFLHYKEKIQEYNV[L]LET[L]-----	
	chicken	134	-----[P]TLDOPRLEKLW[S]KAKTSGKFSDEELDKLWREFKHHKEKIREYNV[L]LET[L]-----	
40	zebrafish	117	-----[P]TFDOPRLEKLW[N]AKTSGKFSDEELQ[TF]HREFQHH[K]D[K]IHEY[N]V[L]MDT[V]-----	
	fruit fly	155	-----[P]HRNKSLSFK[K]KLN[K]LW[E]KEI[SG]F[A]EELKSI[K]Q[E]FDHH[Q]D[K]V[D]VY[Y]SLL[E]N[IG]-----	
	mosquito	165	-----[P]TYKNKSLSFK[K]KLN[K]LWD[K]AE[S]A[TF]KEEL[K]I[RE]EHDH[Q]K[Q]A[K]IDV[Y]SLL[E]R[G]DDDD-----	
	flatworm	118	-----[P]LPSGKFT[QNL]QKLW[SQ]QNGK[FN]QKEI[N]A[H]G[EL]KEVE[Q]KMRV[EDQ]LDFK-----	
45	consensus	181	d DprLekLW KAktsgkFs eELdkLwrEf hhkeKiheYnv[lt]lets	
50	human	195	-----[P]TEEIH[E]M[SP]SPLS-----DTKGSV[H]S[E]HTEL[E]K-----	
	mouse	216	-----[P]AEE[G]YEN[L]I[SP]SDMA-----H[IK]SDT[L]I[S]K[H]SEL[K]D[R]-----	
	rat	195	-----[P]AEE[G]YEN[L]I[SP]SDMT-----H[IK]SDT[L]I[S]K[H]SEL[K]D[R]-----	
	chicken	185	-----[P]TEEIH[K]VNPSEEN-----PVKEEV[H]NKE[RE]LKE[K]-----	
	zebrafish	168	-----[P]TEEIH[K]VNPSEEN-----DVKEV[H]QK[H]TEL[K]ORM-----	
	fruit fly	209	-----[P]TVDT[E]KH[E]NA[TE]ELDTY[N]LISNDVNENDIKTHAQNV[K]SFENDLNT[RGHH]-----	
	mosquito	224	-----[P]GGAAGQGSR[DD]ALLNAV[ND]EEH[D]RYNEV[D]RAEET[D]RSQPGAN[Q]HAYL[H]NSN[Q]LREK[H]-----	
	flatworm	171	-----[P]X-VPHENS[Q]H[DI]ES-----IG-----DTKKLKAAN-----	
55	consensus	241	r ee henvispsdl ik l khteLkek[re]	

human	229	RSINQGLDRLRFVSHQGYSTEAEFEEPRVIDLWDLAQSA-ELIDKELEAFREELKHFEAK
mouse	250	RSINQGLDRLRKVSHQGYGTTAEFEEPRVIDLWDLAQSA-NFTKELESFREELKHFEAK
rat	229	RSINQGLDRLRKVSHQGYGPATEFEEPRVIDLWDLAQSA-NFTKELESFREELKHFEAK
chicken	219	RSINQGFERLRLKVSHQGYDATSEFEEPRVIDLWDLAQSA-NFTKELESFREELKHFEAK
zebrafish	201	PDLNQGFERLRLKITHEGYTDDSEFREPRVIELNEMAKRS-ILSFDELD-LKEELRHFFTK
fruit fly	261	TGIKDHYDRLERLVSSPHQ-DHIEIKVQGLMRVAGAS-NFTVKELESIKTELHSEFESR
mosquito	284	REIRDNEFDRLDRIASKGPKQ-DFVEIKVQGLMRVAGAS-DFSADEIAALKVELLHESR
flatworm	197	REINDHLDEVHRKVTEEFQP-FNEPRVKRLWKLACENEKLTPELSVILKDELSHFESQ
consensus	301	rsinqglrlrrvshqgy s teFeEPrVidLWdlAqsa nftekElesfreELkHfEak
10		
human	288	IEKHNNHYQKOLEISHEKLKHVE-----VGDGERVSRSREKHALLEGETKELGYTVKKHL
mouse	309	IEKHNNHYQKOLEISHEKLKHVE-----IGIPHEHTSRNKEKYVLLEEKTKELGYKVKKHL
rat	288	IEKHNNHYQKOLEISHEKLKHVE-----IGIPHEHTSRNKEKYVLLEEKTKELGYKVKKHL
chicken	278	IEKHNNHYQKOLEISHEKLKHVE-----TGIKEHINRNREKYAMLEEKTKELGYKVKKHL
zebrafish	260	VEKHNNHYQKOLEISHEKLKHVE-----IGIPHEHTSRNKEKYNTLAENAKENEGYKVKKHL
fruit fly	319	LLKLRLHILHAEHALQKNEYKGEK-----VKDKSSRFEEEMEDQLNKQTRAVENLQ
mosquito	342	LLKLRLHMHAIHALSLEKHKHS-----DAKADTHKLMEDNINKQTRAVENLQ
flatworm	255	EKKIEFHKVFFFVANSCPREGKNEEVSRQEDAEERGKDKSQVYENLELSIKHEKLNKA
consensus	361	ieKhnhhyqkqleishekikhve vgd ehv rnreky lleektkelgykvkkhl
20		
human	343	QDLSGRISR--ARHNEEL
mouse	364	QDLSSRMR--ARHNEEL
rat	343	QDLSSRMR--ARHNEEL
chicken	333	QDLSSRISQG-LQHNEEL
zebrafish	315	QDLNPKISQNGLQHNEEL
fruit fly	367	ENIEKTIIFK----HTEL
mosquito	388	EEVERRIIFK----HSEL
flatworm	315	RKLEKYIEEKIIIHREL
30		
consensus	421	qdls risr HnEL

Figure 15: Amino Acid Sequence Of Human RAP (SEQ ID NO:1)

TyrSerArgGluLysAsnGlnProLysProSerProLysArgGluSer
GlyGluGluPheArgMetGluLysLeuAsnGlnLeuTrpGluLysAla
GlnArgLeuHisLeuProProValArgLeuAlaGluLeuHisAlaAsp
LeuLysIleGlnGluArgAspGluLeuAlaTrpLysLysLeuLysLeu
AspGlyLeuAspGluAspGlyGluLysGluAlaArgLeuIleArgAsn
LeuAsnValIleLeuAlaLysTyrGlyLeuAspGlyLysLysAspAla
ArgGlnValThrSerAsnSerLeuSerGlyThrGlnGluAspGlyLeu
AspAspProArgLeuGluLysLeuTrpHisLysAlaLysThrSerGly
LysPheSerGlyGluGluLeuAspLysLeuTrpArgGluPheLeuHis
HisLysGluLysValHisGluTyrAsnValLeuLeuGluThrLeuSer
ArgThrGluGluIleHisGluAsnValIleSerProSerAspLeuSer
AspIleLysGlySerValLeuHisSerArgHisThrGluLeuLysGlu
LysLeuArgSerIleAsnGlnGlyLeuAspArgLeuArgArgValSer
HisGlnGlyTyrSerThrGluAlaGluPheGluGluProArgValIle
AspLeuTrpAspLeuAlaGlnSerAlaAsnLeuThrAspLysGluLeu
GluAlaPheArgGluGluLeuLysHisPheGluAlaLysIleGluLys
HisAsnHisTyrGlnLysGlnLeuGluIleAlaHisGluLysLeuArg
HisAlaGluSerValGlyAspGlyGluArgValSerArgSerArgGlu
LysHisAlaLeuLeuGluGlyArgThrLysGluLeuGlyTyrThrVal
LysLysHisLeuGlnAspLeuSerGlyArgIleSerArgAlaArgHis
AsnGluLeu

Figure 16: Amino Acid Sequence of the 28 kD RAP polypeptide (SEQ ID NO:2)

ProArgLeuGluLysLeuTrpHisLysAlaLysThrSerGlyLysPhe
SerGlyGluGluLeuAspLysLeuTrpArgGluPheLeuHisHisLys
GluLysValHisGluTyrAsnValLeuLeuGluThrLeuSerArgThr
GluGluIleHisGluAsnValIleSerProSerAspLeuSerAspIle
LysGlySerValLeuHisSerArgHisThrGluLeuLysGluLysLeu
ArgSerIleAsnGlnGlyLeuAspArgLeuArgArgValSerHisGln
GlyTyrSerThrGluAlaGluPheGluGluProArgValIleAspLeu
TrpAspLeuAlaGlnSerAlaAsnLeuThrAspLysGluLeuGluAla
PheArgGluGluLeuLysHisPheGluAlaLysIleGluLysHisAsn
HisTyrGlnLysGlnLeuGluIleAlaHisGluLysLeuArgHisAla
GluSerValGlyAspGlyGluArgValSerArgSerArgGluLysHis
AlaLeuLeuGluGlyArgThrLysGluLeuGlyTyrThrValLysLys
HisLeuGlnAspLeuSerGlyArgIleSerArgAlaArgHisAsnGlu
Leu